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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,409	03/12/2001	Timothy J. Kieffer	029996/0278721	1113

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,409	KIEFFER ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-70* is/are pending in the application.

4a) Of the above claim(s) *1-30 and 56-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 16 June 2004 has been entered.

The IDS of 16 June 2004 is considered with this Action.

Claims 1-70 are pending and Claims 1-30 and 56-70 remain withdrawn from prosecution as drawn to non-elected subject matter.

Claims 31-55 are presently considered.

Notification of Examiner Reassignment

Applicant is notified that this Application has been reassigned to Examiner Robert M. Kelly, of Art Unit 1632.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-55 are newly rejected, and Claims 43-44 remain rejected, under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement for reasons of record in the Official Actions of 18 December 2002 (pp. 3-5) and 18 December 2003 (pp. 3-4). The claim(s) contains subject matter which was not described in the specification in such a way

as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The new rejection of Claim 31 (Response to Applicant's Arguments begin on page 4)

The invention of Claims 31 and 38 encompasses any nutrient that induces production of a protein, and any nutrient that increases expression or secretion of a protein.

These agents of these claims are broad in scope, being defined on the basis of their effect, and not on any specific structure. The specification broadly discloses any ingestible or consumable material such as that present in food or drink (e.g., p. 16, lines 1-2).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, various sugars, fats, steroids, and vitamin D, have been disclosed (e.g., pp. 16-17), however such general disclosure does not allow the Artisan to distinguish between the various members of the genera. The specification does not provide any disclosure as to what would have been the required structure which would allow one to distinguish the various species of the genera. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics are that the nutrient increases expression or secretion of a protein (e.g., pp. 19-20).

Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any nutrient that induces production, secretion, or expression of a protein, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Response to Arguments—Claims 43-44

Applicant's arguments filed on 16 June 2004 have been fully considered, but are not found persuasive.

Applicant identifies the rejection as being based on the genus of "variants or subsequences of gut endocrine promoters [that] possess the biological activity of a gut endocrine promoter." Applicant further asserts that the specification adequately describes claims 43-44, and points to case law for guidance, which case law states, variously: written description may be any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention; a written description may be achieved by means of a recitation of structural features common to the

members of the genus; for biological molecules characteristics can include sequence, structure, and length; and written disclosure does not require disclosure of every species of the genus. From this, Applicant's argue that a description of every gut endocrine promoter, variant, or subsequence, is not required to satisfy the written description requirement. (Applicant's Arguments of 16 June 2004, p. 7, third paragraph-p. 8, first paragraph).

Such argument is not persuasive because the Office has not required a description of every promoter, variant, or subsequence. As stated in the Official Action of 18 December 2002, Applicant has not disclosed all sequences (Official Action of 18 December 2002, p. 4) (Note: this does not mean that we are requiring all sequences, it is simply here to elucidate our reasoning.), there is expected variation among the sequences (Id.), the specification discloses various gut endocrine promoters (Id.), but only describes a very few number of variants or subsequences, which actually reduce the activity, indicating that the activity may vary drastically among the variants encompassed (Official Action of 18 December 2003, p. 4), no evidence of record exists with regard to a relationship between the structure of any gut endocrine promoter and the claimed variants and subsequences (Official Action of 18 December 2002, p. 4), the art indicates that there is variation between the gut endocrine promoter DNA sequences (Id.). For these reasons, and the absence of other countervailing reasons, there is no evidence of record that would indicate that any of the claimed variants or subsequences of gut endocrine promoters even have the biological activity required for a gut endocrine promoter (Id.; Official Action of 18 December 2003, p. 4).

Applicant further argues that, having disclosed relevant identifying characteristics of endocrine promoters and enhancers, and elements that are likely to confer activity, one skilled in

the art (hereinafter the "Artisan") would be apprised of gut endocrine promoter and enhancer variants and subsequences. Moreover, Applicant argues, therefore, the Artisan would also know sequences that could be mutated or deleted without destroying activity. Consequently, Applicant argues, the Artisan would know which sequences could tolerate substitutions and deletions without destroying activity and therefore would know of numerous functional variants and sequences. (Applicant's response received 16 June 2004, p. 8, first full paragraph).

Such argument is not considered persuasive. The various members disclosed do not provide a relation between the structure of any gut endocrine promoter and the claimed variants or sequences (Official Action of 18 December 2002, p. 4). As such, from these sequences, the Artisan would not know which variants or subsequence of any specific element would provide the requisite activity, and Applicant's claims do not require such activity, but only a functional variant or subsequence of any of these promoters and enhancers (Id.). Moreover, by only describing a very few number of variants or subsequences of a single promoter, which actually reduce the activity, there exists evidence that the activity may vary drastically among the variants encompassed (Official Action of 18 December 2003, p. 4). For example, although the disclosed variants encompass a few mutations to GIP's GAT motifs, which are limited to proximal and distal locations of the promoter, and even these minor mutations produced different activity levels, the Artisan would not be able to produce even any encompassed variant or subsequence of GIP, much less any variant or subsequence of any element (Id.). Therefore the Artisan would not know numerous functional gut endocrine promoter and enhancer variants or subsequences.

Applicant further argues that GIP TATA boxes, CCAAT-like boxes, AP-1, AO-2, cAMP-RE, a potential insulin-response element, and the disclosed GIP GAT motifs, which may

lower the activity to 35%, would provide the disclosure required for the regions of the GIP promoter that could be varied or deleted and still confer partial activity (Applicant's response of 16 June 2004, last paragraph).

Such argument is not considered persuasive. Applicant's arguments for CCATT-like boxes, and potential insulin-response element demonstrate an absence of knowledge of how these sequences may be mutated and retain the activity required, which activity is still not required by the claims, but simply a general functionality. Moreover, such minor mutations as have been shown provide for greatly reduced activity (up to 65% reduced), and as such the Artisan would not know which other regions could be varied or deleted and still confer activity, even for the GIP element (Official Action of 18 December 2003, p. 4).

Applicant further illustrates the previous argument by stating that that the Artisan would know GIP TATA and CCAAT boxes should not be mutated because the activity of the element would be reduced, but nucleotides outside these boxes could be mutated without destroying promoter function, and therefore, the Artisan would know of GIP promoter variants and subsequences having function (Applicant's response of 16 June 2004, p. 9, first paragraph).

Such argument is not persuasive. Applicant's argument is not consistent with the partial reduction in activity of their own GAT mutants of GIP, which are considered to be functional variants. Hence, some variants of even these elements are encompassed by the claims, but the Artisan would not know, as Applicant states, which variants would be functional.

Applicant further illustrates by way of examples of GIP promoters that the first 193bp of the human GIP and rat GIP promoters confer promoter activity, and that DNAse I footprinting identified CREs, which are essential for basal promoter activity, and as such, the 193bp upstream

sequence is a useful variant or subsequence, and the sequences outside the CRE sequences could be mutated (implying that the CRE sequences could not be mutated).

Applicant further argues that human and rat promoter regions of approximately 193 basepairs upstream the transcription start site are functional and therefore these would be functional subsequences (Applicant's Response of 16 June 2004, p. 9, second paragraph), and further argues that CRE elements at positions –351 and –158 are essential for basal activity of the promoter and as only nucleotides outside these sequences could be deleted or mutated without destroying promoter activity (Id., third paragraph).

Such arguments are not considered persuasive, because, *inter alia*, they conflict with each other, and because the destruction of promoter activity is not what is required, but simply that the sequences are functional. Applicant states that sequences up to about position –193 is a functional subsequence (Id., Second paragraph), while apparently, not every CRE (which CREs are essential for basal promoter activity, Id., third paragraph) are not required because at least one CRE is located at position –351, and hence, would not be in the –193 to +14 fragment of Applicant's stated encompassed functional subsequence (Id., second paragraph).

Moreover, because the claims encompass any functional subsequence and not sequences having the functional activity of GIP, these activities could simply be the function of linking the sequences on either side of the encompassed sequence, and as such, would not require any of the aforementioned sequences characteristics that Applicant maintains are required (Id., pp. 8-9), much less for any nutrient-regulatable element variant or subsequence. Such has been addressed in prior office actions (e.g., Official Action of 18 December 2002, p. 4, lines 14-17). Moreover, although not relied upon for this rejection, Applicant's specification states that "... functional ...,

when used in reference to a nucleic acid ..., subsequence or fragment, ..., means that the sequence has one or more functions of [the] native nucleic acid ...." (Specification, p. 16, lines 21-25). Hence, for example, the function of linking adjacent sequences in the chromosome would be maintained by any sequence, and therefore does not rely on any of Applicant's required structure. Therefore, even if GIP would be considered to have sufficient written description for variants and subsequences of GIP that contain the same activities as that of native GIP, the claims as written do contain such functional language.

Applicant further argues by way of examples of other specific nutrient-regulatable promoters and enhancers, and regions within these promoters and enhancers, which are shown to provide at least part of the endogenous activity, that, with respect to these other promoters, the artisan would have known these elements within each promoter and, as such, written description is adequate for these other promoters, over and above that of GIP (Applicant's response of 16 June 2004, p. 9, last paragraph-p. 12, first full paragraph).

Such argument is not persuasive for the same reasons as given with respect to the GIP promoter. Such evidence of record demonstrates that any particular element within the promoter regions of such polynucleotides may be considered essential for basal promoter activity, and yet may be completely deleted and still be considered a functional subsequence or variant, while others may show drastic differences in activity due to minor mutations (Supra, pp. 6 and 5, respectively). Hence the Artisan would not know which of the variants encompassed produced the requisite activity. Moreover, Applicant's claims only require one or more functions of the native nucleic acids, and therefore, as long as these sequences linked the adjacent sequences, they would be encompassed by Applicants claimed limitation, and therefore, any of Applicant's

above-referenced required sequences would not actually be required. For all of these reasons, and all the reasons of record, it is maintained that the Artisan would not recognize that Applicant was in possession of the necessary common features or attributes possessed by the functional variants or subsequences embraced by the claims.

Accordingly, the previous rejection is maintained for reasons of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-55 remain rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record in the prior Official Actions of 18 December 2002 and 18 December 2003. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Reponse to Arguments

Applicant's arguments filed on 16 June 2004 have been fully considered but are not found persuasive.

Applicant argues that the rejections relate solely to an alleged unpredictability in the art of gene therapy (Applicant's Response of 16 June 2004, p. 12, third paragraph).

Such is not found persuasive. The rejection is based on the breadth of the claims (e.g., Official Action of 18 December 2002, p. 5, third paragraph), the nature of the invention (e.g., Id., pp. 7-9), the state of the prior art (e.g., Id., pp. 9-12), the level of predictability in the art (e.g.,

Id., p. 12, second paragraph), Applicant's provided direction and guidance (e.g., Id., p. 6), Applicant's examples (e.g., Id., p. 13), which would lead to undue experimentation (e.g., p. 12, second paragraph) because such unpredictability exists in the art, and Applicant's disclosure provides no such disclosure to overcome the deficiencies in the art (e.g., Id.). Moreover, all of this considered at the level of ordinary skill in the art, the Ph.D. or M.D. level practitioner, because each of the articles cited is written by Ph.D. and/or M.D. practitioners.

Applicants again argue that the rejection of Claims 31-55 do not require gene therapy, and therefore, the rejection based on gene therapy is improper. Applicant then demonstrates why the claims do not require gene therapy, state that over the full scope of the invention such gene therapy is not required, and further assert that enablement for gene therapy is therefore not required. (Applicant's response of 16 June 2004, p. 12, last paragraph.)

Such arguments are not found persuasive. First, assuming, solely for the sake of argument, that gene therapy was not required for the claims, the claims must be enabled for their making and their use. (MPEP 2106). In order to practice this method, however, in a subject so-transformed with the required polynucleotide would require being able to obtain such subject. The specification, however, provides no disclosure on how such subject may be obtained or even identified from the pool of subjects available. Moreover, the Examiner is aware of no art that provides such information. Hence, even if the claims did not require gene therapy, they would not be enabled for the making because the Artisan would not know how to obtain such materials to practice the invention.

Moreover, method claims require enablement for their full scope (2164.08 [R-1]). The claims require treating a subject **comprising** the contacting of mucosal tissue cells of a patient,

(already transformed with a nucleic acid sequence), with a nutrient that induces production of the protein encoded by the nucleic acid sequence. Such open-ended language as comprising makes these method claims encompass the prior step of so-transforming cells of the subject with the polynucleotide. Hence, these claims do encompass gene therapy (e.g., Official Action of 18 December 2002, p. 6, last paragraph).

Lastly, assuming that the transgenic mouse is being relied upon for such argument (e.g., Official Action of 18 December 2003, p. 5, paragraphs 2-3), the Examiner maintains that the claims as written read on gene therapy, as the subject comprises cells transformed with a heterologous polynucleotide (Id.).

Applicant's restate their previous arguments with respect to the Kieffer declaration submitted with Applicant's Response of 20 June 2003. Specifically, Applicant's assert that such evidence enables treating a disorder by contacting transformed mucosal tissue cells in a subject with a nutrient that induces production of a protein in an amount effective to treat the disorder, as in claims 31-55 (Applicant's Response of 16 June 2004, p. 13, first paragraph).

Such arguments are not considered persuasive for reasons of record. As stated in the Official Action of 18 December 2003, p. 6, paragraph 3:

> The Kieffer declaration under 37 CFR 1.132 filed 6/20/03 is insufficient to overcome the rejection of claims 31-55 based upon enablement as set forth in the last Office [A]ction because: The Kieffer declaration while providing a working example relating to *ex vivo* gene therapy fails to enable the full scope of the claimed methods. The claims are overly broad as they relate to any disease and any therapeutic protein. While the Kieffer declaration provides evidence of treatment of obesity using the ob/ob mouse comprising implanted GC-1pSwitch cells the Kieffer declaration fails to provide evidence of treatment of other diseases embraced by the claims.

Applicant submits the Cheung declaration under 37 CFR 1.132 with Applicant's response of 16 June 2003. (Applicant paraphrases the data and conclusions of the Cheung declaration in Applicant's response of 16 June 2004, pp. 13-14). The Cheung declaration relates to the use of two different vectors to transfer heterologous genes *in vivo* to mucosal tissue. In each of these experiments, the vectors were delivered either by direct injection into the intestinal wall or luminal incubation. While each of these genes delivered remained present in the intestine for up to two weeks, only the c-peptide of insulin was provided for proof of expression of protein. Moreover Dr. Cheung states, "I conclude that transfer of a gene encoding a therapeutic protein into mucosal tissue cells *in vivo* would not require undue experimentation at the time of the invention."

Such declaration is insufficient to overcome to the rejection of claims 31-55 based upon enablement as set for the last Office Action, for reasons of record in the prior Office Actions, because: The Cheung declaration, while offering a working example of the production of a single protein, does not provide any results for the production of any other protein. Moreover, the Cheung declaration does not use promoters responsive to a nutrient. Lastly, Dr. Cheung simply states that transfer of the gene encoding a therapeutic protein into mucosal tissue would not require undue experimentation. Such information does not provide enough evidence, even in light of the Kieffer declaration (p. 11 of the Office Action), to allow the artisan to reasonably predict that by any route of administration, enough of the vector would reach and transform enough target tissue, become stably incorporated, (or enough transformed cells would reach the target site and become part of the tissue), and produce enough stable and functional mRNA, and protein therefrom, and the protein would properly processed and reach their target sites of action

in large enough quantities to effect treatment, for any particular disease (as provided for in the Official Action of 18 December 2002, pp. 5-14). The claims are overly broad as they relate to any disease and any therapeutic protein. While the Cheung declaration provides evidence of production of protein in one example, it is predictable that by any route of administration, enough of the vector would reach and transform enough target tissue, become stably incorporated, (or enough transformed cells would reach the target site and become part of the tissue), and produce enough stable and functional mRNA, and protein therefrom, and the protein would properly processed and reach their target sites of action in large enough quantities to effect treatment, for any particular disease (as provided for in the Official Action of 18 December 2002, pp. 5-14). Lastly, the Cheung declaration does not conclude that enough protein would be produced by these methods to produce a therapeutic effect with regard to any disease.

Applicant summarizes their arguments: (1) Claims 31-55 do not recite a step of transforming and therefore do not require gene therapy, and do not require such enablement; and (2) the data of the Kieffer and Cheung declarations provide adequate enablement, even if they were required to enable gene therapy (Applicant's Response, pp. 14-15, paragraph bridging).

Such arguments are not considered persuasive, for reasons of record, as reviewed above (pp. 9-12).

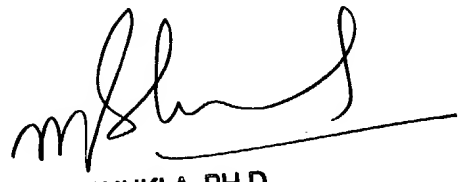
CONCLUSION

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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PRIMARY EXAMINER